REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and the following remarks.

Status of Claims

Claims 1-63, 65-71, 77-93, 95 and 96 are cancelled, without prejudice or disclaimer, and claims 64, 72 and 94 are revised. The amendment to claim 64 is supported by the specification, *e.g.*, at page 5, line 25 to page 6, line 35. Claims 72 and 94 are amended accordingly, to ensure proper antecedent basis. Amended claim 94 also recites a range of molar ratios, 1:14 to 14:1, that tracks the specification at page 17, lines 16-23.

The foregoing amendments do not introduce impermissible new matter, and they comport with the elected group and species. These changes are made solely to advance prosecution, not in acquiescence to any rejection. Upon entry of this response, therefore, independent claim 64 and claims 72-76 and 94 will be pending.

Obviousness Rejection

The examiner has rejected claims 64, 66, 67, 69 – 76, and 93-26 over the combination of U.S. patent No. 5,759,584 (Traupe) and the 1995 article of Shalita *et al.* Applicant traverses the rejection as it may have been applied to pending claims 64, 72-76, and 94.

Applicant reasserts its stated position concerning the impropriety of combining one reference, Traupe, that heralds the use of an agent displaying "antimicrobial action" with another reference, Shalita, that *eschews* "antimicrobials." See Amendment and Reply of January 2, 2009, at pages 8-10. In particular, Shalita teaches that "nicotinamide gel is a desirable alternative treatment for acne vulgaris because antimicrobials ... are associated with resistant microorganism[s] such as Proprionibacterium" (action at page 7, second paragraph). Accordingly, it would run contrary to the central purpose of Shalita's disclosure to bring nicotinamide together an active agent, such 1-glyceryl monocaprylate, that is known to "display an antimicrobial action," per Traupe (column 3, last paragraph), even as to Propionibacterium.

On page 2 of the action, the examiner responds, citing to Eady, that the antibiotic resistance demonstrated by Shalita "has only been demonstrated by the antibiotics erythromycin, clindamycin, tetracycline, trimethorprim, and doxycycline." Thus, the examiner is heard to argue that antibiotic resistance has been demonstrated only for a restricted number of antibiotics, per Eady, and that Shalita therefore cannot be relied upon for a teaching away as to *all* antibiotics. This is not correct, however, as shown by the Eady reference itself. In particular, page 556 of Eady, at column 1, states that "[m]inocycline is the only antiacne antibiotic to which cutaneous propionibacteria have not acquired resistance, although it is widely prescribed." Thus, Eady shows that resistance was seen against *all but one* of the antibiotics commonly prescribed for acne. Accordingly, Eady actually supports applicant's assertion that Shalita teaches away from the use of antimicrobials because of the risk of widespread resistance, already a reported phenomenon by 1993.

In addition, Shalita expresses concern about resistance caused by antimicrobials in general, *i.e.*, both antimicrobials already known to cause resistance ***and*** antimicrobials potentially causing resistance in the future. This is further emphasized in the "Conclusion" paragraph of the Abstract, which states that, "[b]ecause topical clindamycin, like other antimicrobials, is associated with emergence of resistant microorganisms, *nicotinamide gel is a desirable alternative treatment for acne vulgaris*" (emphasis added). In other words, Shalita teaches away from using not only antimicrobials already known to cause resistance but also <u>other antimicrobials</u> as well. This interpretation comports in fact with Eady *et al.*, "Antibiotic-resistant propionibacteria in acne: Need for policies to modify antibiotic usage," *BMJ* 306: 555 (1993), which the examiner has cited. Eady discusses guidelines for treatment of acne in the second to last paragraph: "We recommend the following guidelines for antibiotic treatment of acne in both hospital and general practice. *Firstly, do not prescribe antibiotics if a non-antibiotic topical preparation will suffice*" (emphasis added).

It is apparent, therefore, that both Eady and Shalita teach away from the use of *any* antimicrobial. By the same token, both teach away from combining niacinamide with glyceryl caprylate, which Traupe clearly characterizes. as anti-microbial,

The examiner also argues that

> ...it would be expected that the combination of nicotinamide with 1-glyceryl monocaprylate would exhibit at least an additive effect in treating acne. Thus, any alleged side effects from the 1-glyceryl monocaprylate could be minimized by using a lower dosage of 1-glyceryl monocaprylate while still achieving the same acne treating effect.

Office Action at page 3. The argument that one could have expected a specific result, and could have minimized any negative side effects, does not find support in any way in the Shalita or Traupe, even *if* one were to ignore the clear teaching away by Shalita. Instead, the examiner's perspective is grounded entirely on a hindsight, which is impermissible for a sustainable obviousness analysis.

Because the examiner has failed to sustain the *prima facie* case, the pending obviousness rejection should be reconsidered and withdrawn. Even were a *prima facie* case established, however, such a case would be rebutted by applicant's evidence of unexpected results. The examiner argues at page 4 of the action that the evidence of unexpected results is "not commensurate with the breadth of the claims." This remark was made in the context of the previously pending claims which encompassed a large genus of acyl fatty acids, fatty acid derivatives, and their salts; *and* a large genus of niacinamide salts and derivatives. The presently pending claims recite glyceryl monocaprylate and niacinamide, and their respective salts. Applicant submits, therefore, that the present claims ***are*** commensurate with the breadth that the examiner recognizes on page 4 of the action.

In this regard, applicant has shown that a combination of glyceryl octanoate (glyceryl monocaprylate) and niacinamide exhibits unexpected results in suppression of hypersensitivity and inflammatory reactions. Illustrative in this regard were the results obtained with "Compound 51," and "Compound 107" in Examples 111 and 112, which yielded a statistically significant and dose-dependent inhibition of ear oedema. This was surprising in at least two ways. First, the anti-inflammatory effect was 65% higher than the additive effect of the individual active components of the complex, and thus is a surprising and novel synergy. Second, the anti-inflammatory effect was comparable to the effect of betamethasone 17-valerate, one of the strongest topical steroids on the market, and which had been applied at the maximal human clinical dose. This finding is very surprising and demonstrates that it is possible to obtain an

anti-inflammatory effect comparable to a strong steroid with substances that are virtually non-toxic and do not induce any of the damaging effects to the skin caused by corticosteroids like betamethasone 17-valerate. The posited Traupe/Shalita combination does not demonstrate such surprising results.

In regards unexpected results, pages 3 and 4 of the action state:

> ...it is the applicant's burden to demonstrate unexpected results over the prior art. Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. Moreover, evidence as to any unexpected benefits must be "clear and convincing" and be of a scope reasonably commensurate with the scope of the subject matter claimed.

(Citations omitted.) In response, applicant notes that Examples 111 and 112 demonstrate that the claimed combination is effective in treating inflammatory disease, as shown with statistical significance in an animal model, and is comparable to a known anti-inflammatory agent. Further, the results observed in the animal model of inflammatory disease were confirmed with human clinical studies, which demonstrated that the claimed composition was clinically effective in treating moderate to severe seborrheic dermatitis (see Example 115).

Applicant believes that these results are demonstrably of "statistical and practical significance" and that the evidence in this regard is "clear and convincing."

The significance of unexpected results to an obviousness analysis was emphasized in *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), when the Court explained that "[t]he combination of familiar elements . . . is likely to be obvious when it does no more than yield predictable results." *KSR*, at 1739. Accordingly, a finding of obviousness is improper where, as here, the claimed invention *does* yield unexpected results. Moreover, objective criteria of nonobviousness, such as unexpected results "is not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness" that must be given full consideration. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008).

Such surprising results are objective evidence that rebuts any asserted *prima facie* case of obviousness, and further establishes the non-obviousness of claims 64, 72-76 and 94. Applicant

believes, therefore, that pending claims 64, 72-76 and 94 are unobvious for the foregoing reasons. Accordingly, reconsideration and withdrawal of the rejection are requested.

Claim 94 is *separately* patentable over the prior art because the Traupe/Shalita combination does not teach the surprising result observed with glyceryl monocaprylate and niacinamide in a molar ratio of between about 1:14 to 14:1. Illustrative of this ratio are Examples 111 and 112, showing surprising results within the claimed range. According to commentary on page 6 of the Office Action, however"

> ...it would be obvious to one of ordinary skill in the art at the time of the invention to optimize the ratio of 1-glycerol monocaprylate to niacinamide as claimed in the instant claims 71 and 93-96. Proportions of ingredients, to impart patentability to an otherwise obvious chemical composition, must produce more than ***a mere difference in degree*** in the properties of the composition.

(Emphasis added.) Yet, the presently claimed composition displays an effectiveness that is comparable to the highest dose of one of the strongest anti-inflammatory steroids known. To characterize this as a "mere difference in degree" does an injustice to the significance of the observation.

The examiner's minimization of the importance of surprising results is contrary to law, moreover, as it is "not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness" that must be given full consideration, according to *Ortho-McNeil Pharm.* 520 F.3d 1365.

Applicant also disagrees with the assertion on page 6 that "it would [have been] obvious ... to optimize the ratio of 1-glycerol monocaprylate to niacinamide as claimed in the instant claims 71 and 93-96," especially as it may have been applied to present claim 94. In *Takeda Chem. Industs., Ltd. v. Alphapharm Pty, Ltd.*, 492 F.3d 1350 (2007), the Federal Circuit invoked *KSR* in finding non-obviousness in claims that were directed to a specific chemical compound, where "the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." The court emphasized that obviousness requires that the prior art give a reason or motivation to make the specific composition claimed. 492 F.3d at 1356. Thus, the mere fact that one *may* optimize a given combination of elements is insufficient without a reason or suggestion leading towards the composition of claim 94.

In this regard, applicant notes that Traupe says nothing about anti-inflammatory properties for glycerol monocaprylate. By the same token, nothing reasonably gleaned from Traupe and Shalita together could have provided a reason or suggestion to "optimize" some anti-inflammatory effect, even if one somehow were suspected, in the combination of niacinamide and glycerol monocaprylate. Thus, the Traupe/Shalita combination does not suggest an enhanced anti-inflammatory property, does not provide the person of ordinary skill with the reason or suggestion to optimize the combination for *anti-inflammatory* effects, nor does it provide any direction towards the specific range recited in claim 94.

In view of the foregoing, applicant asserts that claims 64, 72-76 and 94 are not obvious and, therefore, that the rejection should be withdrawn.

CONCLUSION

Favorable reconsideration of this application is respectfully requested. Examiner Karol is invited to contact the undersigned directly, should she feel that any issue warrants further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, then applicant hereby petitions under 37 C.F.R. §1.136 for such extension and authorizes payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

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